CLINICAL RESEARCH

Randomised trial of prophylactic daily aspirin in British male doctors

R PETO, R GRAY, R COLLINS, K WHEATLEY, C HENNEKENS, K JAMROZIK, C WARLOW, B HAFNER, E THOMPSON, S NORTON, J GILLILAND, R DOLL

Abstract

A six year randomised trial was conducted among 5139 apparently healthy male doctors to see whether 500 mg aspirin daily would reduce the incidence of and mortality from stroke, myocardial infarction, or other vascular conditions. Though total mortality was 10% lower in the treated than control group, this difference was not statistically significant and chiefly involved diseases other than stroke or myocardial infarction. Likewise, there was no significant difference in the incidence of non-fatal myocardial infarction or stroke—indeed, disabling strokes were somewhat commoner among those allocated aspirin. The lower confidence limit for the effect of aspirin on non-fatal stroke or myocardial infarction, however, was a substantial 25% reduction. Migraine and certain types of musculoskeletal pain were reported significantly less often in the treated than control group, but as the control group was not given a placebo the relevance of these findings was difficult to assess. There was no apparent reduction in the incidence of cataract in the treated group.

The lack of any apparent reduction in disabling stroke or vascular death contrasts with the established value of antiplatelet treatment after occlusive vascular disease.

University of Oxford

R PETO, MA, MSC, Imperial Cancer Research Fund reader in cancer studies
R GRAY, MSC, research officer
R COLLINS, MB, MSC, British Heart Foundation senior research fellow
K WHEATLEY, PHD, research officer
C HENNEKENS, MD, associate professor of medicine
K JAMROZIK, MD, lecturer in medicine
C WARLOW, MD, professor of medical neurology
B HAFNER, member of permanent staff
E THOMPSON, data manager
S NORTON, data manager
J GILLILAND, data manager
SIR RICHARD DOLL, FRCP, FRS, emeritus professor of medicine

Correspondence to: Mr R Peto, Clinical Trial Service Unit, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford OX2 6HE.

Introduction

Aspirin, even in small amounts, may completely inhibit cyclo-oxygenase dependent platelet aggregation in vitro, suggesting that it may have a clinically useful antithrombotic effect in vivo. Randomised trials of daily aspirin were therefore undertaken in the late 1960s for the prevention of venous thrombosis and in the early 1970s for the prevention of arterial thrombosis. By the late 1970s an overview of trial results had shown that daily aspirin could definitely reduce the risk of reinfarction in the months or years after recovery from a myocardial infarction.[1] Hence it seemed likely that prophylactic daily aspirin would also prevent some thrombotic events among apparently healthy people with no overt history of cardiac or cerebrovascular disease, though it was not known how great any such effect might be, nor how prolonged it would be, nor whether it would be outweighed by any adverse effects. To answer these questions direct evidence was needed from randomised controlled trials of prophylactic aspirin.

Vascular events in apparently healthy people are not common even in middle and old age, so that even if prophylactic aspirin reduced their incidence by about a quarter—that is, roughly the same reduction as after myocardial infarction—this could be determined reliably only by trials including some tens of thousands of subjects followed up for several years. Two large studies of prophylactic aspirin were therefore undertaken, one among British doctors and the other, about four times as large, among Americans. Doctors were thought to be particularly suitable for these trials because of their particular ability to appreciate what is entailed and to judge the potential risks and benefits that may be associated with the prophylactic use of aspirin. Doctors should, moreover, be able to provide particularly accurate information about any non-fatal illnesses that they may suffer. This paper reports the results of the British trial.

Subjects and methods

In 1978 an invitation to collaborate was sent to all male doctors resident in the United Kingdom who were born this century, who had replied to a questionnaire about their smoking habits that was sent to them in 1951 (as part of another study), and who were still listed in the 1977 *Medical Directory*. The next year a similar invitation was sent to all such doctors who

had not replied to the 1951 questionnaire and 15% (n=762) more joined the study. Most of the 20 000 or so doctors approached would have liked to participate but many were ineligible: some were already taking aspirin for various reasons, some could not take it, and others gave a history of peptic ulcer, stroke, or definite myocardial infarction which excluded them from the study. The remaining 5139 doctors were recruited, almost half of whom were under 60 in 1978.

Treatment was scheduled to continue from November 1978 (or, for the 762 doctors who joined later, from November 1979) to November 1984, and our principal analysis of death and of other outcomes included all events occurring within this scheduled treatment period and none thereafter. Two thirds of the doctors were randomly allocated by computer to take daily aspirin (500 mg ordinary, soluble, or effervescent aspirin, as desired, or, if subsequently requested, 300 mg enteric coated aspirin) unless some contraindication was thought to have developed, and one third were randomly allocated to avoid aspirin and products containing aspirin unless some specific indication for aspirin was thought to have developed. It was suggested that paracetamol be used initially if an analgesic was required. Placebo tablets were not used, so that treatment was not blind. (Allocation in the ratio 2:1 was to facilitate later subdivision of the active treatment group into two dose levels; this, however, was not pursued.)

All participating doctors were asked to complete a brief questionnaire every six months about their health and their use of aspirin or other antiplatelet agents over the preceding six months. Information was specifically requested about possible myocardial infarctions, strokes, and transient ischaemic attacks and further details sought from the participants or their treating physicians about any that were reported. This information was first screened to remove any indication of which treatment group the participant had been in and then examined by a cardiologist or neurologist in Oxford, who classified the reported myocardial infarctions, strokes, and transient ischaemic attacks as definite, probable, or doubtful; the last category was excluded from most analyses. Though information was sought about the likely aetiology of any strokes, the lack of computed tomography meant that a firm distinction between cerebral infarction and primary intracerebral haemorrhage was possible in only a minority of cases; most cases of subarachnoid haemorrhage, however, were probably diagnosed reliably.

Deaths in Britain were discovered partly by replies from relatives to correspondence, partly from the records of the General Medical Council, and partly by flagging National Health Service records at the Office of Population Censuses and Surveys. Whenever possible certified causes of death recorded as vascular were supplemented by scrutiny of clinical or other records, but in practice this led to hardly any changes. Deaths abroad were few, and their circumstances were sought by correspondence. Deaths and the various non-fatal events reported by the subjects were coded according to the ninth revision of the International Classification of Diseases (ICD) with minor modifications for external causes of death. All deaths and any non-fatal vascular events were coded by medically qualified staff and other non-fatal events (and details of compliance reported by the subjects) by non-medical staff, except when uncertainties arose. At the end of the study a further questionnaire was sent to all surviving participants, which, in addition to checking that no principal event (that is, myocardial infarction, stroke, or transient ischaemic attack) had been missed, also asked specifically about peptic ulcer, migraine, and cataract. This was completed either directly or by telephone for 99% of all surviving participants.

STATISTICAL METHODS

Statistical analyses principally consisted in simple comparisons of the proportions of affected subjects in the treated and control groups. More elaborate time to death analyses, based on the log rank test[2] with stratification for any of the minor imbalances in baseline features between those allocated to take aspirin and those allocated to avoid it, generally yielded almost identical results and are not presented here.

Twice as many subjects were allocated to take aspirin as were allocated to avoid it, so that direct comparison of the uncorrected numbers of events recorded would be inappropriate. Hence most results are tabulated as first event rates per 10 000 subject years alive in the study, which allows simple, direct comparison of event rates between the two groups. As the controls were followed up for a total of about 10 000 man years, the actual number of controls who developed a particular condition was numerically similar to the rate per 10 000 years tabulated. (This can be used to help statistically inclined readers estimate the extent to which control rates might be subject to random variation.)

Inevitably a proportion of subjects originally allocated daily aspirin stopped taking it for medical or other reasons. All were followed up, however, as we could not assume that those who stopped were medically comparable with those who continued. Any important difference would bias comparison of the controls with subjects in the treatment group who continued with aspirin, as there was no way to distinguish those controls who would have continued to take aspirin from those who would not. Moreover, many of the doctors in the control group who began taking aspirin regularly did so because some vascular disease had developed. To avoid any possibility of bias[2] our tests of whether there was any real effect of aspirin were chiefly based on an "intention to treat" comparison of all those originally allocated to the control group with all those originally allocated aspirin, irrespective of whether they actually took it regularly.

Results

Altogether 5139 eligible doctors agreed to be randomly allocated either to take aspirin daily or to avoid aspirin. Baseline characteristics were generally evenly balanced between the two groups with the exception of prerandomisation systolic blood pressure, which was 1 mm Hg higher (p=0·05) in the group allocated aspirin (table I). During the first year after randomisation 661 (19%) of the 3429 doctors allocated to take aspirin stopped doing so, and during the subsequent five years a further 5% of those originally allocated to aspirin stopped each year (table II). Thus halfway through the study roughly 70% of doctors who had been allocated aspirin were still taking it on most days. Gastrointestinal symptoms were the principal medical reason given for stopping aspirin, and in a few cases symptoms appeared to be alleviated by switching to enteric coated tablets (300 mg). In the group allocated to avoid aspirin an additional 2% or so of the subjects in each year of the study began to use it (either regularly or irregularly), often because vascular disease had developed. Effectively, therefore, the study assessed the effects of about two thirds more of the treated than control group taking aspirin regularly. Data on mortality were thought to be complete and data on morbidity virtually complete.

Myocardial infarction—No significant differences in the rates of fatal or definite non-fatal myocardial infarction were detected between the two

TABLE I—*Baseline characteristics of study groups at entry. Except where stated otherwise figures are numbers (percentages) of doctors*

	Group allocated aspirin	Group allocated to avoid aspirin (controls)
No of participants	3429	1710
Age (years):		
<60	1604 (46·8)	804 (47·0)
60-69	1349 (39·3)	658 (38·5)
70-79	476 (13·9)	248 (14·5)
Smoking:		
Always non-smoker	859 (25·1)	395 (23·1)
Ex-smoker	1512 (44·1)	776 (45·4)
Current smoker, cigarettes only <20/day	224 (6·5)	123 (7·2)
Current smoker, cigarettes only ≥20/day	205 (6·0)	109 (6·4)
Other, or mixed, current smoker	625 (18·2)	307 (18·0)
Systolic blood pressure (mm Hg):		
<130	816 (23·8)	473 (27·7)
130-149	1235 (36·0)	584 (34·2)
>149	612 (17·8)	288 (16·8)
Not known	766 (22·3)	365 (21·3)
Mean (SE) pressure (mm Hg)	136·1 (0·29)*	135·1 (0·41)*
History of:		
Heart disease other than myocardial infarction	217 (6·3)	102 (6·0)
Angina	83 (2·4)	31 (1·8)
Transient ischaemic attack, etc†	92 (2·7)	44 (2·6)
Hypertension	349 (10·2)	159 (9·3)
Diabetes	69 (2·0)	32 (1·9)
Other vascular disease	111 (3·2)	76 (4·4)

*Difference=2 SE, p=0·05; all other differences not conventionally significant.
†Any cerebrovascular disease other than stroke.

TABLE II—*Numbers (percentages) of doctors allocated aspirin who gave it up*

Principal reason for stopping aspirin	During first year after randomisation	During subsequent five years†
Gastrointestinal bleed	39 (1·1)	30 (1·1)
Dyspepsia	340 (9·9)	200 (7·3)
Constipation	36 (1·0)	47 (1·7)
Bleed/bruising	38 (1·1)	68 (2·5)
Other medical	41 (1·2)	90 (3·3)
Unknown	176 (5·1)	244 (8·9)
Total stopped in treatment group	670 (19·5)	678 (24·8)
Denominator for above figures	3429 (100·0)	2738 (100·0)
(Total started in control group)	(30 (1·8))	154 (9·2)

†Four years for the 762 (15%) doctors who joined in November 1979.

groups (tables III and IV). Nevertheless, despite six years of follow up of over 5000 subjects the total numbers of events were comparatively small (137 deaths from heart disease plus 121 confirmed non-fatal myocardial infarctions). Consequently the 95% confidence interval for the effect of daily aspirin on total (fatal plus non-fatal) myocardial infarctions was wide, ranging from 24% more to about 27% fewer definite infarctions associated with allocation to the treatment group.

Cerebrovascular events—Daily aspirin significantly ($p<0.05$) and substantially (by about half) reduced the frequency of confirmed transient cerebral ischaemic attacks. Nevertheless, a small and non-significant excess of strokes was reported in the group allocated aspirin, with similar patterns for fatal and non-fatal events. The 95% confidence interval for the estimated difference in the incidence of stroke was, however, wide, running from a 25% reduction to a 50% increase. Adjustment for the slight imbalance in prerandomisation blood pressure between the two groups made very little difference. Given the limited data available on which of the strokes were haemorrhagic and which thrombotic, it appeared only that aspirin was not associated with a significant excess of any particular type of stroke. Participants who suffered a stroke were more likely to describe it as disabling if they were in the group allocated aspirin. Though this may reflect more severe strokes in these subjects, perhaps due to haemorrhage, some bias may have been introduced by the subjective nature of the assessment of residual disability and by the lack of placebo control.

Deaths—Non-vascular death rates were 15% lower (122/3429 *v* 72/1710) in the aspirin group than in the control group, but this difference was not conventionally significant. It was chiefly due to a shortfall of more than half in mortality from acute respiratory disease and a slight shortfall in deaths from cancer, but these unanticipated differences may well represent data-derived fluctuations due to chance. Overall vascular death rates (including sudden death from unknown causes and peptic ulcer and gastric haemorrhage) were 6% lower (148/3429 *v* 79/1710; NS) in the aspirin group than in the control group. Of the non-stroke deaths, few were ascribed to causes related to bleeding, and among these there was no excess associated with aspirin.

Other events—Non-fatal peptic ulcer disease was reported significantly more often by subjects taking aspirin and there was also a slight excess of non-fatal gastric bleeds reported, but these excesses did not correspond with increases in mortality from these causes. Migraine attacks for which medical attention was sought and various forms of musculoskeletal pain for which attention was sought were reported significantly less often by those allocated aspirin. There was no apparent difference between the two groups in the incidence of cataract.

TABLE III—*Cause specific death rates by allocated treatment*

Underlying cause of death (and ICD category (9th revision))	Deaths/10 000 man years†	
	Group allocated aspirin (n=3429; subject years=18 820)	Controls (n=1710; subject years=9470)
Definite myocardial infarction or stroke	63·2	62·3
410-414 Myocardial infarction	47·3	49·6
430-432 Haemorrhagic stroke	5·3	4·2
433-434 Occlusive stroke	4·3	3·2
Rest 430-439 Stroke, unknown aetiology	6·4	5·3
Other vascular and related causes	15·4	21·2
394-397 Rheumatic endocardial	1·6	0
Rest 390-399 Other rheumatic disease	0	0
400-409 Hypertensive disease	1·1	2·1
415 Pulmonary embolus	2·1	0
416 Respiratory heart disease	0·5	1·1
421, 424 Non-rheumatic endocardial	1·1*	5·3*
Rest 417-429 Other heart disease	3·2	3·2
441 Aortic aneurysm	2·1	4·2
Rest 440-459 Other vascular	1·1	1·1
530-535:		
Gastric haemorrhage	0·5	0
Peptic ulcer (haemorrhagic)	0	3·2
Peptic ulcer (perforated)	1·1	0
797-799 Unknown‡	1·1	1·1
Remaining (non-vascular) causes	64·8	76·0
150-152 Cancer of upper digestive tract	5·8	5·3
162 Cancer of lung	7·4	11·6
Rest 140-239 other neoplasms	26·6	31·7
460-489 Acute respiratory disease	4·3*	11·6*
490-519 Chronic respiratory disease	4·3	4·2
All other diseases	9·0	6·3
External causes (accidents, etc)	7·4	5·3
Total (all causes)	143·5	159·5

*2p<0·05.
†Estimated as number of deaths divided by 1·882 or 0·947.
‡Deaths from unknown causes all occurred abroad; anecdotal evidence suggests that all were vascular.

TABLE IV—*Rates of certain non-fatal vascular and non-vascular events by allocated treatment*

Non-fatal adverse events	First events/10 000 man years†	
	Group allocated aspirin (n=3429; subject years=18 820)	Controls (n=1710; subject years=9470)
Vascular and related conditions		
Non-fatal myocardial infarction:		
Confirmed myocardial infarction	42·5	43·3
Possible myocardial infarction	11·7	4·2
Non-fatal stroke:		
Confirmed stroke	32·4	28·5
(Disabling+other)	(19·1*+13·3)	(7·4*+21·1)
Probably haemorrhagic	1·6	2·1
Probably occlusive	6·9	4·2
Unknown aetiology	23·9	22·2
Possible stroke	3·2	3·2
Transient ischaemic attack:		
Confirmed transient ischaemic attack	15·9*	27·5*
Possible transient ischaemic attack	5·3*	14·8*
Bleed, not cerebral	10·6	7·4
Other vascular conditions:		
Hypertension	227·9	216·5
Arrhythmias	140·8	137·3
Acute thrombotic event (pulmonary, venous, or other)	52·1	59·1
Other	96·7	100·3
Peptic ulcer	46·8*	29·6*
Non-vascular events		
Non-fatal malignant neoplasm	63·2	61·2
Respiratory:		
Acute infections	149·3	162·6
Chronic bronchitis, emphysema	27·6	30·6
Asthma	33·5	42·2
Cataract	86·1	77·1
Migraine	197·1***	276·7***
Musculoskeletal disorders for which medical advice sought	544·1***	639·9***

Note: Non-fatal occurrences of a particular disease exclude occurrences in patients who later died of that disease.
*2p<0·05; **2p<0·01; ***2p<0·001.
†Estimated (without use of life table methods) as number of subjects ever affected divided by 1·882 or 0·947.

Discussion

Our principal hope when we began this study was that vascular events and vascular death might be avoided. In this respect the results are not encouraging, though the confidence intervals for the effect of treatment on stroke, myocardial infarction, or vascular death are wide (ranging between a 16% benefit and a 26% adverse effect). Total mortality was somewhat less in subjects allocated aspirin, but the excess number of fatal or disabling strokes is disturbing. A review by the Antiplatelet Trialists' Collaboration (see accompanying paper) has shown that allocation to antiplatelet treatment of patients known to be at particular risk of thrombotic events (because of preceding events such as transient ischaemic attacks, minor strokes, unstable angina, or myocardial infarctions) reduces the incidence both of non-fatal strokes and of non-fatal myocardial infarctions and significantly reduces vascular mortality, with no apparent adverse effect on non-vascular mortality. After allowing for the effects of non-compliance that review suggests that actual use of aspirin in such patients would yield reductions in non-fatal events and vascular death of about one third and one sixth respectively. Our study, however, does not provide a final balance of the exact benefits and hazards of prophylactic aspirin among apparently healthy people, possibly because no material effect existed or possibly because the total numbers of such events were small and hence unduly subject to chance. Reliable information about prophylaxis for apparently healthy people is unlikely to become available until our results on over 5000 British doctors can be considered in conjunction with the corresponding results from the study of prophylactic aspirin among 22 000 doctors in the United States and with any other relevant evidence.

Preliminary results from the trial in the United States have just been made available,[3] well before its scheduled end in 1990, because they currently indicate that allocation to aspirin has averted more than one third of all non-fatal myocardial infarctions. In contrast, the unpromising results of the trial in the United Kingdom suggest

that prophylactic aspirin had no effect and cannot have averted much more than a third of all non-fatal myocardial infarctions. The United States trial, however, observed about three times as many non-fatal myocardial infarctions as the United Kingdom trial did, so the positive result from the United States carries more weight than the null result from the United Kingdom. If, therefore, the truth lies somewhat nearer to the United States than to the United Kingdom result then taken together these two primary prevention trials suggest that prophylactic antiplatelet treatment can probably avert about one third of all non-fatal myocardial infarctions. Such a reduction is plausible, for it is similar to the reductions of 35% and 31% in non-fatal myocardial infarction suggested by the overviews of results of antiplatelet trials in patients with cerebral and with cardiac vascular disease (see accompanying paper). But although a reduction in non-fatal myocardial infarction must presumably correspond to some reduction in fatal myocardial infarction, it does not necessarily correspond to a net reduction in overall vascular mortality. At present, neither the United States nor the United Kingdom trial results suggest any reduction whatever in overall vascular mortality, and both suggest some increase in the number of disabling strokes (which, in the United States trial, were attributed to cerebral haemorrhage).

Side effects of aspirin may be assessed in an unbiased way only with placebo control, so the present data on side effects add little to the data from the main placebo controlled studies.[4,5] The adverse effects on the stomach and oesophagus of daily doses of 1000 mg aspirin found in placebo controlled studies are appreciable but may largely be avoided by reducing the amount or frequency of dosage (UK-TIA Study Group trial, accompanying paper) or using an enteric coated aspirin preparation (which should dissolve in the intestine but not in the stomach). Some protection against various aches and pains was expected, but the reduction in the numbers of subjects reporting migraine on the final questionnaire was substantial and would presumably have been somewhat larger (that is, over 30%) had compliance with the allocated treatment been greater. Because of the lack of placebo control, however, this finding needs support, possibly from a placebo controlled prophylactic study in migraine clinics of the extent to which recurrence of migraine could be avoided (or its symptoms controlled) by some regimen such as 300 mg enteric coated aspirin daily. A small placebo controlled trial of aspirin in migraine sufferers found about a 50% reduction in headaches, but only 12 patients were studied.[6] The lack of support for suggestions that aspirin might help avoid cataract is similar to the findings in some[7] but not all[8] case-control studies. Conversely, the apparent shortfall in both fatal and non-fatal respiratory diseases offers no support to the suggestion that aspirin might aggravate such conditions.[9]

Thus though the prophylactic use of daily aspirin for "secondary" prevention of disease among patients at high risk of thrombotic disease has been shown to reduce the incidence both of non-fatal vascular events and of vascular death, and though it is still possible that apparently healthy people will, when fuller evidence is available, be found to derive comparable proportional reductions in risk, our study has provided no definite indication that any such benefits exist.

By far the greatest acknowledgment is to the doctors who participated in this study. In Oxford Brian Gribbin, Jane Kench, Gale Mead, David Skegg, Steve Sutherland, and Salim Yusuf helped in many different ways. The Aspirin Foundation (G N Henderson, G Fryers) provided financial support but with its ready agreement had throughout no contact with the study's conduct, results, or interpretation.

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United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results

UK-TIA STUDY GROUP

Abstract

From 1979 to 1985, 2435 patients thought to have had a transient ischaemic attack or minor ischaemic stroke were allocated at random to receive long term blind treatment with either aspirin 600 mg twice daily (n=815), aspirin 300 mg once daily (806), or placebo (814). Treatment continued with about 85% compliance until September 1986 (mean four years). The odds of suffering one or more of four categories of event—namely, non-fatal myocardial infarction, non-fatal major stroke, vascular death, or non-vascular death—were 18% less in the two groups allocated to receive aspirin than in the group allocated to receive placebo (2p=0·01). The more relevant but less frequent composite event of disabling stroke or vascular death was reduced by only 7%; this reduction was not significantly different from zero, but nor was it significantly different from a 25% reduction. There was no definite difference between responses to the 300 mg and 1200 mg daily doses, except that the lower dose was significantly less gastrotoxic.

University of Oxford
Participants in the trial are listed at the end of this paper.

Correspondence and requests for reprints and copies of the protocol to: UK-TIA Study Group, Clinical Trial Service Unit, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford OX2 6HE.

Introduction

Patients who have had a transient ischaemic attack or have largely recovered from an ischaemic stroke are at risk not only of a recurrence but of a permanently disabling or fatal vascular event. The natural course of transient ischaemic attack and of mild ischaemic stroke is similar[1]; the subsequent incidence of stroke (about 4% a year) is the same as that of myocardial infarction (in-